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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,173	06/24/2004	Katsuhito Takahashi	4439-4022	3299

27123 7590 10/18/2006
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EXAMINER

POPA, ILEANA

ART UNIT PAPER NUMBER

1633

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/500,173

Applicant(s)

TAKAHASHI ET AL.

Examiner

Ileana Popa

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 July 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 1, 3-24, 26, and 29-36 have been amended. No new matter was introduced by these amendments. Claim 2 has been cancelled.

Claims 1 and 3-36 are pending and under examination.

Note: Change of Examiner

The Examiner of record is now Ileana Popa, Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE and the Art Unit.

Response to Arguments

Specification

3. Acknowledgment is made of the Applicant's amendment to the abstract to contain less than 150 words and to the drawings, which are submitted as replacement sheets. Accordingly, the objections to the abstract and to the drawings are withdrawn.

4. The objection to specification is maintained for the reasons of record set forth in the previous Office Action.

Applicants traversed the instant objection on the ground that they are entitled to be their own lexicographers and request the deferral of the expense of re-translating the application until further prosecution on the merits has occurred.

Applicant's arguments filed 07/21/2006 have been fully considered but they are not persuasive. The specification was objected to because of improper English translation and arrangement, and not because Applicants acted as their own lexicographers (i.e., impart a novel meaning to terms well accepted in the art and redefined the terms by setting forth definitions of the terms that are different from their ordinary and customary meaning). However, upon Applicants request, the submission of a re-translated version of the specification is deferred.

Claim Objections

5. The objection to claims 8-36 under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim is withdrawn in response to Applicants amendments to the claims filed on 07/21/2006.

6. The objection to claims 1-7 for being presented in non-idiomatic English is withdrawn in response to Applicants amendments to the claims and cancellation of claim 2, on 07/21/2006.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. The rejection of claims 1-7 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicants amendments the claims and cancellation of claim 2 on 07/21/2006.

Claim Rejections - 35 USC § 112 - enablement

8. The rejection of claim 2 under 35 U.S.C. 112 for not complying with the enablement requirement is withdrawn in response to Applicants cancellation of the claim on 07/21/2006.

9. Claims 1 and 3-7 remain rejected under 35 U.S.C. 112 for not complying with the enablement requirement for the reasons of record set forth in the prior Office Action. Applicant's arguments filed 07/21/2006 have been fully considered but they are not persuasive.

Applicants traversed the instant rejection on the grounds that Yamamura et al. (Applicants' IDS), and also cited in the instant specification, show that the region including the sequence from -260 to -219 shown in SEQ ID NO: 1 is an essential region for the regulation of transcriptional initiation of the calponin gene promoter.

Contrary to Applicants' assertions, although Yamamura et al. teach that the sequence between positions -260 and -219 is essential for the positive control of calponin gene transcription in HOS (osteosarcoma) and HMC (mesangial) cell lines, they do not teach that this region can by itself promote tissue specificity. There is a

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difference between positive regulation of transcription and tissue/cell specificity. Absent evidence to the contrary, the sequence between positions -260 and -219 can perform equally well in different tissues/cells and it is possible that additional regions of the calponin promoter are required to confer tissue/cell specificity. Yamamura et al. teach that the sequence between positions -260 and -219 includes consensus-binding sites for Sox and GATA-1 transcription factors. However, these factors can control transcription from a variety of promoters in different cell and tissue types. Yamamura et al. do not teach that they are indeed implicated in conferring tissue/cell specificity for the calponin promoter. The cited art does not teach, and Applicant did not demonstrate, that SEQ ID NOs: 1 and 2 are sufficient to confer tissue/cell specificity and that other regions of the calponin promoter are not important for promoting this specificity. Therefore, the specification provides enough of a disclosure to enable for an HSV vector comprising the tissue/cell specific promoter set forth by SEQ ID NO.: 3 and not for any other vector comprising SEQ ID NO: 1 or 2, or variants with unspecified number of deletions, substitutions or additions.

Claim Rejections - 35 USC § 102

10. The rejection of claims 1 and 6 under 35 U.S.C. 102(b) as being anticipated by Martuza et al. (U.S. Patent No. 5,728,379) is withdrawn in response to Applicants amendment to claim 1 filed on 07/21/2006.

Claim Rejections - 35 USC § 103

11. The rejections of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Martuza et al., in view of Yamamura et al. (Cancer Res, May 2001, 61: 3969-3977) or over Takahashi, in view of Martuza and Yamamura, are withdrawn in response to Applicants cancellation of the claim on 07/21/2006.

12. Claims 1 and 3-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al., in view of Yamamura et al. for the reasons of record set forth in the prior Office Action. Applicant's arguments filed 07/21/2006 have been fully considered but they are not persuasive. Additionally, the declaration under 37 CFR 1.132 filed 07/21/2006 is insufficient to overcome the rejection of claims 1 and 3-7 based upon Martuza et al., in view of Yamamura et al. as set forth in the last Office action because for the reasons presented below.

Applicants traversed the instant rejection on the grounds that Martuza et al. fail to provide any information on making HSV strains that carry an intact TK gene with the claimed SEQ ID NOs. Applicants argue that one of skill in the art would have not been expected to have a reasonable expectation of success in making the claimed invention based on the combined teachings of Martuza et al. and Yamamura et al. because, at the time the invention was made, Martuza et al. did not teach homologous recombination of ICP4 gene linked to a cell-specific promoter at the ribonucleotide reductase locus, while preserving endogenous TK. Applicants continue arguing that they were the first to perform the separation of the ribonucleotide reductase deletion

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mutants having ICP4 gene linked to a cell specific promoter by using the method as described in claim 35 of the invention (see declaration under 37 CFR 1.132).

In response to the arguments above, claims 1 and 3-7 do not recite a vector wherein the ribonucleotide reductase gene is deleted, nor do they recite separation of the mutants. The instant claims are drawn to a vector comprising the calponin promoter upstream to a pre-determined gene, wherein the vector does not replicate in normal differentiated cells, and wherein the vector further comprises the 4F2 enhancer upstream of the calponin promoter and the TK gene. Martuza et al. teach an HSV vector, wherein a cell-specific promoter drives the expression ICP4 (i.e., a pre-determined gene), wherein the HSV vector does not replicate in the normal differentiated cells, and wherein the HSV vector contains the intact TK gene (column 4, lines 40-59, column 11, lines 4-16, column 25, lines 39-56). Martuza et al. do not teach the calponin promoter or the 4F2 enhancer (it is noted that the claims are enabled only for a vector comprising the calponin promoter set forth in the SEQ ID NO.: 3, see above). Yamamura et al. teach the calponin promoter and the 4F2 enhancer. It would have been obvious to one of skill in the art, at the time the invention was made, to use the calponin promoter together with the 4F2 enhancer in the vector of Martuza et al., with a reasonable expectation of success. The motivation to use the calponin promoter is provided by Yamamura et al., who teach that calponin is aberrantly expressed in a variety of human soft tissue and bone tumors and therefore, the calponin promoter could be used to target therapeutics to the human soft and bone tumor cells expressing calponin (Abstract, p. 3969, column 2, p. 3976, column 1). The motivation to use the

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4F2 enhancer is also provided by Yamamura et al., who teach that insertion of the 4F2 enhancer upstream of the calponin promoter increases the transcriptional activity of the promoter (p. 3972, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making such a vector because the art teaches that such vectors can be successfully made. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

13. The rejection of claims 1 and 3-7 under 35 U.S.C. 103(a) as being unpatentable over Takahashi (PGPUB 2004/0197308), in view of Martuza and Yamamura, is withdrawn in response to Applicants arguments filed on 07/21/2006.

Double Patenting

14. The provisional rejection of claim 2 for obviousness-type double patenting over Takahashi (U.S. Application 10/477,797), in view of Martuza et al., is withdrawn in response to Applicants' cancellation of claim 2 on 07/21/2006.

15. Claims 1 and 3-7 remain provisionally rejected for obviousness-type double patenting over Takahashi (U.S. Application 10/477,797), in view of Martuza et al., for the reasons of record set forth in the previous Office Action.

Applicant has requested that the obvious-type double patenting rejections set forth by the Examiner be held in abeyance. The Applicants' comments are

acknowledged, however the rejection will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

New Rejections

Claim Rejections - 35 USC § 112

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

16. Claims 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-13 recites the limitation "desired protein" in claim 1. There is insufficient antecedent basis for this limitation in the claim. Amending the claims to reflect proper dependency on claim 9 would obviate this rejection.

17. Claims 21 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps disclosing how the suppression of viral expression/replication is achieved.

18. Claims 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between

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the elements. See MPEP § 2172.01. The omitted elements are: proliferating tumor cells with disrupted proliferating activity as a result of viral replication inside these cells.

Claims 29 and 30, reciting a therapeutic method for fibrosis and malignant tumors, wherein the "proliferating myofibroblast is selectively disrupted as a result of replication of the vector", are unclear. It is not clear, from the language of the claim how inhibition of myofibroblast proliferation leads to cancer therapy.

19. Claims 29-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

20. Claims 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 and the dependent claim 36 are indefinite because the preamble of claim 35 recites "a method for producing a vector ", whereas the body of the claim is drawn to a method of obtaining a single clone by limiting dilution. It is noted that claim 35 contains no method steps disclosing how the vector is produced. Since it is not clear whether the claim is drawn to a method of producing a vector or to a method of cloning

a cell comprising the vector, the metes and bounds of the claim cannot be determined and the claim is indefinite.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

22. Claims 1, 3-7, 14, 16-20, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chung et al. (J Virol, 1999, 73: 7556-7564), in view of Yamamura et al.

* Since the claims are enabled for an HSV vector comprising the tissue/cell specific promoter set forth by SEQ ID NO.: 3 (see above), the instant rejection is applied to the extent that the claims read on SEQ ID NO.: 3, which comprises SEQ ID NO.: 1 and SEQ ID NO.: 2.

** Claims 26-28 are included in the instant rejection to the extent that they read on the claimed vector and not on therapy.

Chung et al. teach an HSV vector comprising the cell cycle regulated B-myb promoter integrated upstream of the predetermined viral gene γ 34.5 (i.e., a viral replication-related gene) and an intact thymidine kinase (tk) gene, wherein the HSV vector does not replicate in the normal, differentiated cells (claims 1, 3-5, 14, 16, and 17) (Abstract, p. 7556, column 2, last paragraph, p. 7558, Fig. 1, p. 7561, column 2, p.

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7563, column 1), wherein the vector comprises a deletion of the gene encoding the viral ribonucleotide reductase and wherein the B-myb promoter- γ 34.5 sequence is inserted in the ribonucleotide reductase locus (claim 19) (p. 7558, Fig. 1, p. 7557, column 1, second paragraph and column 2, *Results*). Chung et al. teach that the vector is specific for cycling cells, i.e., the vector is specific for proliferating cells, such as tumor (claim 18, (p. 7556, column 2, second paragraph, p. 7562, column 2, last paragraph) and that the vector has *in vivo* anticancer effects when tested in a mouse model, i.e., Chung et al. teach a method for the expression/replication of the vector encoding for the replication-related gene (claim 20) (p. 7560, column 2). Chung et al. do not teach the calponin promoter as set forth in SEQ ID No.: 3 or the 4F2 enhancer (claims 6 and 7).

Yamamura et al. teach a replication competent HSV vector comprising the calponin promoter as set forth in SEQ ID NO.: 3 and the 4F2 enhancer upstream of it, wherein the vector inhibits the growth of human soft and bone tumor growth in experimental animals (Abstract, p. 3969, column 1, p. 3972, column 1, p. 3973, columns 1 and 2, p. 3974, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector of Chung et al. by replacing the B-myb promoter with the calponin promoter/4F2 enhancer of Yamamura et al., with a reasonable expectation of success. The motivation to replace the B-myb promoter with the calponin promoter is provided by Yamamoto et al., who teach that calponin is aberrantly expressed in a wide variety of human soft tissue and bone tumors and therefore, the calponin promoter could be used to target therapeutics to the human practically any soft or bone tumor cell (Abstract, p. 3969, column 2, p. 3976, column 1).

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The motivation to use the 4F2 enhancer is also provided by Yamamoto et al., who teach that insertion of the 4F2 enhancer upstream of the calponin promoter increases the transcriptional activity of the promoter (p. 3972, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making such a vector because the art teaches that such vectors can be successfully made. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

23. Claims 1, 3-18, 20-22, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Meir et al. (PGPUB 2005/0074430), in view of both LaFace (U.S. Patent No. 6,649,158) and Yamamura et al.

* Since the claims are enabled for an HSV vector comprising the tissue/cell specific promoter set forth by SEQ ID NO.: 3 (see above), the instant rejection is applied to the extent that the claims read on SEQ ID NO.: 3, which comprises SEQ ID NO.: 1 and SEQ ID NO.: 2.

** Claims 26-28 are included in the instant rejection to the extent that they read on the claimed vector and not on therapy.

Van Meir et al. teach an adenoviral or HSV vector that selectively replicates into hypoxic tumor cells (i.e., the vector does not replicate in normal, differentiated cells), wherein the vector comprises a hypoxia-responsive elements operably linked to a promoter integrated upstream of a gene encoding for a protein that modulates viral replication, such as E1A, and an intact *tk* gene that allows for the termination of viral propagation with an exogenous agents such as ganciclovir (claims 1, 3-5, 14-18, 21, 22,

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and 25) (Abstract, p.1, paragraph 003, p.3, paragraph 0020, p. 7, paragraphs 0071 and 0074, p. 7, paragraph 0069). Van Meir et al. teach that the viral vector can further comprise a DNA encoding for a therapeutic molecule downstream of the E1A gene (claim 8), such as an anti-angiogenic factor, (i.e., the DNA encodes for a proteins that can suppress angiogenesis, cancer metastasis, and cancer growth, as recited in claims 11-13) (p. 3, paragraphs 0020, 0022, and 0023) or an pro-apoptotic factor (claim 10) (p.8, paragraph 0089). Van Meir et al. also teach that the vector has *in vivo* anticancer effects when tested in a mouse model, i.e., Van Meir et al. teach a method for the expression/replication of the vector encoding for the replication-related gene (claim 20) (Example 15). Van Meir et al. do not teach the calponin promoter as set forth in SEQ ID No.: 3 or the 4F2 enhancer (claims 6 and 7). Yamamura et al. teach a replication competent HSV vector comprising the calponin promoter as set forth in SEQ ID NO.: 3 and the 4F2 enhancer upstream of it, wherein the vector inhibits the growth of human soft and bone tumor growth in experimental animals (Abstract, p. 3969, column 1, p. 3972, column 1, p. 3973, columns 1 and 2, p. 3974, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector of Van Meir et al. by replacing the their promoter with the calponin promoter/4F2 enhancer of Yamamura et al., with a reasonable expectation of success. The motivation to replace the B-myb promoter with the calponin promoter is provided by Yamamoto et al., who teach that calponin is aberrantly expressed in a wide variety of human soft tissue and bone tumors and therefore, the calponin promoter could be used to target therapeutics to the human practically any soft or bone tumor cell regardless

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whether they are hypoxic or not (Abstract, p. 3969, column 2, p. 3976, column 1). The motivation to use the 4F2 enhancer is also provided by Yamamoto et al., who teach that insertion of the 4F2 enhancer upstream of the calponin promoter increases the transcriptional activity of the promoter (p. 3972, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making such a vector because the art teaches that such vectors can be successfully made. With respect to the limitation of the DNA encoding for the therapeutic protein being linked to E1A DNA via an IRES (claim 9), this is not innovative over the prior art. The prior art teaches that expression vectors may be used to induce expression of more therapeutic proteins from the same promoter by linking the transgenes to be expressed via IRES elements (see LaFace, column 10, lines 19-27, column 15, lines 25-50). Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

24. Claims 1, 3-7, 14, 16-20, and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chung et al. taken with Yamamura et al., as applied to claims 3-7, 14, 16-20, and 25-28 above, in further view of Tjuvajev et al. (Cancer Res, 1998, 58: 4333-4341, Abstract).

Chung et al. taken with Yamamura et al. do not teach detecting the *in vivo* distribution of the vector by determining tk activity using positron emission tomography (PET) and FIAU labeled with ^{124}I (claims 23 and 24). Tjuvajev et al. teach the noninvasive imaging of *tk* gene transfer and expression by PET and FIAU labeled with ^{124}I . It would have been obvious, to one of skill in the art, at the time the invention was

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made, to monitor the distribution and expression of the vector taught by Chung et al. taken with Yamamura et al., by using PET and FIAU labeled with ^{124}I , with a reasonable expectation of success. The motivation to do so is provided by Tjuvajev et al., who teach their method as useful for providing the information necessary for monitoring clinical gene therapy. One of skill in the art would have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of the method to monitor transgene expression. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Claim Rejections - 35 USC § 112 - enablement

25. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

26. Claims 26-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

* The instant claims 26-28 are drawn to a therapeutic drug against a variety of proliferative diseases/disorders. Such language directed to a therapeutic drug against a disease/disorder is considered to embrace a composition efficient enough such that, when administered to a subject, the treatment of the subject having a condition

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associated with the composition is achieved. Accordingly, preamble language directed to "a therapeutic drug against" taken together with the disclosure of only one intended use that is therapeutic treatment of proliferative diseases/disorders, is considered to require support as outlined in 35 U.S.C. § 112 first paragraph such that therapeutic benefit is considered to be enabled for one seeking to make and use such a composition.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The Breadth of the Claims

The instant claims are drawn to a method of treating a wide range of cancers and other disorders associated with cell proliferation by contacting the subject with a vector comprising an intact *tk* gene and the calponin promoter upstream of a pre-determined gene, wherein the vector is replicated in proliferating cells and wherein, upon its replication, the vector suppresses cell proliferation. The specification teaches that there

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are no particular limitations for the pre-determined gene as long as it is a gene necessary to initiate or maintain viral replication.

The aspects considered broad are: (i) the range of proliferative disorders to be treated, and (ii) the range of vectors used to treat the proliferative disorders.

When read in light of the specification, the breadth of the claimed vectors clearly embraces chromosomes, episomes, liposomes, and any known virus. When introduced into cells, the vector is capable to selectively disrupt malignant cell proliferation, i.e., the vector must be an oncolytic vector. However, unless the vector is derived from a virus, it is not clear how it would work. More specifically, it is not clear how a chromosome, episome or liposome comprising the calponin promoter upstream to a gene capable to promote viral replication and an intact *tk* gene would be able to act like an oncolytic virus and suppress malignant cell proliferation.

The wide range of cancers and other disorders associated with cell proliferation is not limited in any way by the specification, and in fact encompasses distinct diseases that are caused by different genetic factors and result in different clinical manifestation. For example, the term embraces all forms of soft tissue and bone cancer, disorders associated with an overgrowth of connective tissue, such as various fibrotic conditions, including lung and liver fibrosis, or disorders associated with an overgrowth of mesangial cells, such as glomerulonephritis.

As such, the as-filed specification attempt to claim that the disclosed vector, as listed above, can be employed as a master drug to treat practically any cell proliferative disorder.

As will be shown below, these broad aspects are not enabled.

The Nature of the Invention

The nature of the invention is a method of treating cancer and fibrosis by using an oncolytic vector specifically targeted to proliferating cells.

The nature of such invention is within the broad genera of gene therapy for proliferative disorders and gene therapy for proliferative disorders does not generally enable Applicants' invention due to problems with the complexity and unpredictability of such disorders and, also due to problems with using oncolytic vector-based therapies.

Susceptibility and outcome in complex proliferative disorders such as cancer are determined, at least in part by genetic polymorphism, and considerable difficulties remain in elucidating how many genes determine a particular phenotype. The etiology of cancer is multifactorial, and it is likely to involve the actions of genes at multiple levels along the multistage carcinogenesis process. How will therapeutic apply in these cases? A polygenic disease such as cancer may require more than one pharmacological agent for treatment. The use of single agents may often not work very well, due to the complexity of regulatory pathways. Borisy et al. (Proc Natl Acad Sci USA, 2003, 100: 7977-7982) teach:

"[p]atients with infectious diseases and with cancer have benefited from combination chemotherapy, where combinations of drugs are in many cases the standard of care".

Reviewing current strategies available for cancer, El-Aneed et al. (European Journal of Pharmacology, 2004, 498: 1-8) teach:

"Due to the complex nature of cancer, cancer gene therapy includes many therapeutic strategies.

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It is expected, however, that successful cancer treatments will combine traditional therapies such as surgery, chemotherapy, and/or radiotherapy along with single or multiple gene treatments. The ultimate goal of these treatments is to eradicate cancer via various methods and effective therapies."

Proliferative diseases are multifactorial in nature and require more than one agent for treatment. Keith et al. (Nature Reviews, 2005, 4: 1-8) teach:

For most human diseases, there are no magic bullets. The more we learn about the genomic and molecular underpinnings of disease processes, the more apparent this conclusion becomes. Many diseases with a high incidence in the population, such as diabetes, heart disease, cancer, arthritis, asthma and depression, have a multifactorial basis that involves both genetic and environmental risk factors."

Even assuming that the claimed oncolytic vector alone would be sufficient for treatment, the problems with using these vectors for therapy still need to be overcome.

For example, Everts et al. (Cancer Gene Therapy, 2005, 12: 141-161, Review) teach:

"Although the oncolytic potency of both unmodified and genetically engineered viruses has been demonstrated in preclinical studies, the use of oncolytic viruses in destroying tumors in clinical trials has in most cases not yet been very successful.

The idea of using viruses to destroy tumor cells is tantalizing for the simplicity of its principle, and for the perspective it raises. Unfortunately, their effective application is not as straightforward as we would have hoped for. Although preclinical studies are quite promising, data from clinical trials are far less convincing. Although the overall safety of viral treatment was demonstrated, in most cases no objective antitumor responses were evidenced."

Hence, from the nature of the invention, the Artisan would not reasonably predict that the oncolytic viral vector claimed by the instant application could be used to treat proliferative disorders in general.

The State of the Prior Art and the Level of Predictability in the Art

Applicants' claims encompass the use of oncolytic viruses to inhibit proliferation of malignant cells. The problems of oncolytic viral vectors based therapies are well

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known in the art, particularly with regard to the viral delivery, the immune responses that can antagonize the effectiveness of the virus, systemic distribution and intratumoral spread, such that the virus can reach the target to a degree necessary to result in a therapeutic effect. Routes of administration, virus stability, and specific delivery are critical for the success of a therapy method. With respect to administration routes, Meng et al. (Gene Therapy of Cancer, Chapter 1, 1999, pp. 3-20) teach that other than intratumor injection, delivery of virally expressed genes by intravascular or intracavitary injections also presents barriers fore therapy (p. 6, column 1). For example, Meng et al. state:

"In intravascular administration, instillation into a peripheral vein dilutes the vehicle, so only a small portion may ultimately reach the tumor. Intravascular administration also elicits a powerful immune response. Tropism for organs such as the liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous if the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass. In the case of intracavitary administration (i.e., intrapleural or intraperitoneal), the surface of the tumor mass is coated by virus, but intratumoral delivery within a solid mass represents an important barrier"

Along these lines, Everts et al. teach:

"Furthermore, efficient viral spread within a tumor has been recognized as one of the most important parameters for antitumor efficacy following i.t. or systemic treatment. However, viral spread in solid tumors *in vivo* is often limited. Possibly, ineffective viral spread might relate to the relative large size of the viruses (for example, 90 and 120 nm for adenovirus and HSV-1, respectively), mixture of the tumor cell mass with normal cells (up to half of the cells in some tumors) or low expression of receptors needed for viral infection.

Another factor that could potentially limit efficient tumor cell killing by oncolytic viruses in cancer patients is the heterogeneity of tumor cell populations. As a result, it is likely that oncolytic viruses are able to kill some tumor cell populations more efficiently than others."

With respect to viral stability and specific delivery, Vargese et al. (Cancer Gene

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Therapy, 2002, 9: 967-978, Review) teach:

“Rapid inactivation of the virus due to instability (virus half-lives), adsorption, and homing to non-specific cells; clearing by the liver; innate immunity; preexisting immunity (antibodies) leading to complement-mediated inactivation; and lack of tropism are issues that merit continued research”.

In view of the reasons set forth above and of numerous issues, as indicated above, which need to be overcome in order to achieve the broadly claimed objective of the claimed subject matter, a skilled artisan would reasonably conclude that the state of the art of therapy by employing oncolytic viruses to treat any cell proliferative disorder, remains reasonably unpredictable at the time of filing.

The Amount of Direction or Guidance/The Existence of Working Examples

Given the breadth of the claimed invention, and the complexities associated with the nature of the claimed invention, one skilled in the art would have to turn to the specification for guidance. However, as indicated above, and even assuming that the level of one skilled in the art is relatively high in the prior art, the guidance provided by the specification is not sufficient to overcome the doubts and obstacles expressed in the art of record. As such, the only issue left is the working examples provided by the specification. The specification provides examples of experiments in nude mice, wherein transplanted tumor growth is inhibited by the administration of an HSV-1-based oncolytic vector.

These examples do not appear to reasonably render the claimed invention as a whole patentable under 35 USC, 112, first paragraph, particularly given the doubts expressed by numerous cited art, as indicated above. Although the prior art

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teaches that oncolytic viral vectors are able to inhibit cell proliferation in cell cultures and in animal models, it is not apparent how this reasonably correlates with a successful therapy in humans. The problems with animal-based models are well known in the art, particularly with regard to forecasting aspects such as predicting the clinical outcome (see above). For example, such animal models have the potential to be misleading, as the molecular pathways important for tumor growth in these models may be different from those in humans (see above).

Van Dyke et al. (Cell, 2002, 108: 135-144) teach:

"However, a common feature of many mouse tumor models is that they represent mainly the early stages of disease development and relatively few recapitulate the features of advanced human cancer, including high frequency metastasis."

As such, the specification fails to teach one of skill in the art how to overcome the unpredictability of oncolytic vector targeting such that efficient therapy is achieved by a generic viral vector and a generic route of delivery of a viral construct as claimed for the treatment of a number of proliferative cell related diseases as contemplated by the as-filed application.

Conclusion

Thus, the specification is not enabling for a therapeutic method of a broad range of proliferative diseases by using a vector comprising an intact *tk* gene and the calponin promoter upstream of a pre-determined gene, wherein the vector is replicated in proliferating cells and wherein, upon its replication, the vector suppresses cell proliferation. While the intent is not to say that oncolytic viruses can never be used to treat cell proliferative disorders, the intent is to provide art taught reasoning as to why

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the instant claims are not enabled.

Conclusion

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

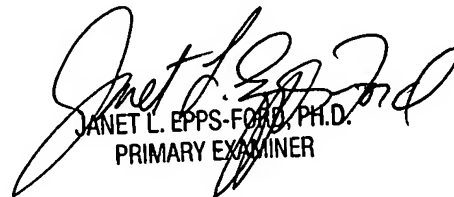
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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